# Justification of Dibasic Esters (DBE) Category and Overview of DBE Robust Summaries

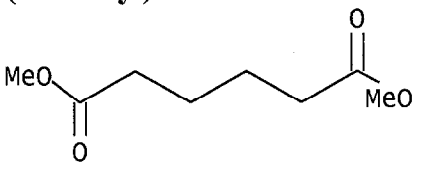
## Introduction

The Dibasic Esters (DBE) Category represents three refined dibasic ester solvents: Dimethyl Adipate (DMA), Dimethyl Glutarate (DMG), Dimethyl Succinate (DMS) and the mixture of these three compounds (DBEs)[1]. DBE[2], the primary product, is distilled to produce six DBE fractions for specialty applications (DBE-2, DBE-3, DBE-4, DBE-5, DBE-6, DBE-9). Fractions DBE-4, DBE-5, and DBE-6 are the pure dimethyl esters DMS, DMG, and DMA, respectively. Fractions DBE-2, DBE-3, and DBE-9 are atypical mixtures of the three dimethyl esters used in specialty applications. DBEs are clear, colorless liquids, having a mild, agreeable odor. They are readily soluble in alcohols, ketones, ethers, and many hydrocarbons, but are only slightly soluble in water and higher paraffins. They are used as solvents (e.g., industrial coatings, industrial cleaners, paint removers, inks), plasticizers, polymer intermediates and specialty chemical intermediates. Exposure to DBEs from these uses, specifically paint stripping, has been evaluated by the US EPA (1994).

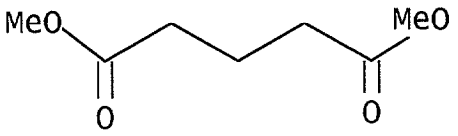
DBE is presented as a Category based upon the similarities of DMS, DMG, and DMA in structures (see structures below), physicochemical properties (Table 1), and consistent responses in ecotoxicology (Tables 3 and 4) and human health toxicology (Table 5 and 6) studies. The Category includes four Robust Summaries, the three individual dimethyl esters, DMS (CAS# 106-65-0), DMG (CAS# 1119-40-0), and DMA (CAS# 627-93-0) and the mixture DBE (CAS# 95481-62-2).

## Structures of Three Dibasic (Dimethyl) Esters

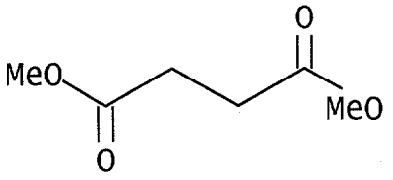
Dimethyl Adipate




Dimethyl Glutarate




Dimethyl Succinate




[1] DBEs are also referred to as DMEs (Dimethyl Esters), but DBE is designation in this document.
[2] A mixture of three dimethyl esters, DMA, DMG, and DMS at proportions ranging from 10-25, 55-65, and 15-25 percent, respectively.

DMS, DMG, and DMA are highly similar in structure differing by only one alkyl carbon. These compounds are the dimethyl esters of four, five and six carbon dicarboxylic acids, succinic, glutaric and adipic acids, respectively. The close structural similarity, combined with similar test results, is the basis for the DBE Category.

**Availability of Data for SIDS Data Elements**

Four separate robust summaries are provided in support of the DBE Category. Table 2, below, shows that most of the SIDS data elements are addressed for one or more of the individual DBEs or the mixture. For many of the data elements, acceptable data are available for all four members of the category. Data are available for at least one chemical in the category in all 20 data elements. Data are available for all four DBEs for 14 of 20 data elements. As shown in Table 2 the robust summaries for DBE, DMS, DMG, and DMA are nearly complete.

**Correlation of Physicochemical properties**

Reported values for physicochemical properties are presented in Table 1 with data for DBE (column 2) and the three dibasic esters (DMS, DMG, and DMA). With the exception of melting point and partition coefficient, the values for physicochemical properties demonstrate a progressive pattern (positively or negatively correlated) related to molecular weight of the three dimethyl esters (DMS. DMG, and DMA). The DBE values are generally intermediate in the range of values for DMS, DMG, and DMA. The ranges of values observed for individual properties are small. The consistency of the relationships among these four chemicals is strong and supports the appropriate development of the DBE Category.

**Correlation of Ecotoxicity Data**

Ecotoxicology data are presented in Table 3. Comparison of available data for ecotoxicity shows DBEs are "slightly" to "practically non-toxic" to fish and aquatic invertebrates. $LC_{50}$ or $EC_{50}$ values for fish, invertebrates, and algae range from: 50-100 mg/L to 25.7 mg/L, 497 mg/L to 3,317 mg/L, and 4.4 mg/L to 11.9 mg/L, respectively. These values appear to be correlated with a gradient in solubility for the three, dimethyl esters (Table 2) and inversely correlated with the molecular weights. The data for all three ecotoxicology data elements further support the development of a DBE category.

## Table 1: Comparison of Physicochemical Properties For DBE and Three Dibasic Esters[a]

| Physicochemical Properties | DBE[b] (Mixture) | DMS (DBE-4) | DMG (DBE-5) | DMA (DBE-6) |
|---|---|---|---|---|
| | 95481-62-2 | 106-65-0 | 1119-40-0 | 627-93-0 |
| Molecular Weight (g/M) | 159 | 146 | 160 | 174 |
| Melting Point ($^oC$) | -20[c] | 19[c] | -37[c] | 8.5[c] |
| Boiling Point ($^oC$) | 196-225[d] | 196[d] | 213.5-214[d] | 230.9[d] |
| Density | 1.092[d] | 1.11[d] | 1.0876[d] | 1.062[d] |
| Vapor Pressure (Torr @ 20$^oC$) | 0.2[d] | 0.9[d] | 0.1[d] | <0.05[d] |
| Partition Coefficient | 0.19[d] | 0.19[d] | 0.62[e] | 1.03[e] |
| Water Solubility (wt. %) | 5.3[d] | 7. 5[d] | 4.3[d] | 2.4[d] |
| Flash point ($^oC$) | 100 (212)[d] | 94 (200)[d] | 107 (225)[d] | 119 (235)[d] |

[a]Adapted from Dupont Co. (1994). Technical Information: Dibasic Esters (DBE) with the exception of Partition Coefficient that was taken from the robust summaries for the respective DBEs. [b] A mixture of three dimethyl esters, DMA, DMG, and DMS at proportions ranging from 10-25, 55-65, and 15-25 percent, respectively, [c] ND = not determined, [d] Measured values, [e] Calculated values.

### Correlation of Acute Toxicity Data

Acute toxicity studies (oral toxicity, dermal toxicity, skin irritation and eye irritation) for four test materials (DBE, DMA, DMG and DMS) were conducted by the DBE Group. These studies were conducted in the same laboratory under the same test conditions, and results are compared in Table 4, below. The results are essentially the same for dermal toxicity, skin irritation and eye irritation (BioDynamics 1992a,b,c,d,e,f,g,h,i,j,k,l,m,n,o,p). Acute oral toxicity values vary above and below the highest exposure level of 5000 mg/kg. Reported $LD_{50}$ values for rats from previous studies with DBE (8191 mg/kg) (Dupont Co. 1981) and DMS (>5,000 and 6892 mg/kg) (IUCLID 2000) were >5,000 mg/kg consistent with the most recent studies with the other DBE materials The results of these studies show a high level of consistency for acute toxicity between the four chemicals in the DBE Category.

### Correlation of Results from Repeated-Dose Studies

As shown in Table 5, subchronic (90-day) inhalation studies have been conducted at varying levels of exposure for all four chemicals in the DBE Category. DMG and DBE were evaluated at a range of exposure concentrations and show a similar dose response. All four DBEs have been evaluated at the nominal exposure level of 400 $mg/m^3$ and effect levels are compared where a dose response is available (Table 6). The major effect observed for all four materials is an increase in degeneration of rat nasal epithelium. Where other effects were observed, similar patterns are observed for DMS, DMG, and DMA. The consistent pattern of response in these subchronic exposures (Table 6) indicates that a valid chemical category exists for these materials.

## Table 2: Availability of Data for Each SIDS Data Element for the DBE Category Including DBE and Three Individual Dimethyl Esters

| No. | SIDS Data Elements | DBE 95481-62-2 | DMA 627-93-0 | DMG 1119-40-0 | DMS 106-65-0 |
|---|---|---|---|---|---|
| **Physicochemical Properties** | | | | | |
| 1 | Melting Point | v | v | v | v |
| 2 | Boiling Point | v | v | v | v |
| 3 | Vapor Pressure | v | v | v | v |
| 4 | Partition Coefficient | v | v | v | v |
| 5 | Water Solubility | v | v | v | v |
| 6 | Flashpoint | v | v | v | v |
| **Environmental Fate** | | | | | |
| 7 | Photodegradation | v | v | -- | v |
| 8 | Stability in Water | -- | v | -- | -- |
| 9 | Transport (Fugacity) | -- | v | v | v |
| 10 | Biodegradation | v | v | v | v |
| 11 | Bioconcentration | -- | v | v | v |
| **Ecotoxicology** | | | | | |
| 12 | Acute Toxicity to Fish | v | v | v | v |
| 13 | Acute Toxicity to Daphnia | v | v | v | v |
| 14 | Acute Toxicity to Aquatic Plants | -- | v | v | v |
| **Mammalian Toxicology** | | | | | |
| 15 | Acute Toxicity | | | | |
| a | o Acute Oral Toxicity | v | v | v | v |
| b | o Acute Dermal Toxicity | v | v | v | v |
| c | o Acute Inhalation Toxicity | v | -- | -- | -- |
| d | o Skin Irritation | v | v | v | v |
| e | o Eye Irritation | v | v | v | v |
| 16 | Repeated Dose Toxicity | | | | |
| a | o Oral | v | -- | -- | -- |
| b | o Inhalation | v | v | v | v |
| 17 | Developmental Toxicity | v | v | -- | -- |
| 18 | Reproductive Toxicity | v | v | v | v |
| 19 | *in vivo* Genotoxicity | v | -- | v | v |
| 20 | *in vitro* Genotoxicity | v | v | v | v |

**Conclusions**

The conclusion of this data analysis for four DBE materials (DBE, DMS, DMG, and DMA) is that a DBE Category is justified. The very consistent pattern of structural and physicochemical properties and results of biological and toxicological studies support this conclusion. The use of a DBE Category, combined with the relatively complete matrix of SIDS data elements, indicates that there is no additional testing required (See Test Plan).

## Table 3: Comparison of Ecotoxicity Data for DBE and Component Dibasic Esters

| Test organism | DBE | DMS | DMG | DMA |
|---|---|---|---|---|
| Fish (96-h $LC_{50}$) (mg/L, ppm) | >18 and <24 (slightly toxic) | 50-100 (slightly to practically non-toxic) | 30.9 (slightly toxic) | 25.7 (calc.) (slightly toxic) |
| *Daphnia magna*[a] (48-h $EC_{50}$) (mg/L, ppm) | 136; >112 and <150 (practically non-toxic) | 3,317 | 1,275 | 497 |
| Green algae (96-h $EC_{50}$) (mg/L, ppm) | -- | 11.9 | 7.2 | 4.4 |

[a] Two separate *D. magna* studies are available for DBE and both show highly consistent results.

## Table 4: Comparison of Acute Toxicity Data for DBE and Three Individual Component Dimethyl Esters[a]

| Test | DBE | DMS | DMG | DMA |
|---|---|---|---|---|
| Rat Oral Toxicity (mg/kg) | >500 and <5,000 | >500 and <5,000 | >5,000 | >5,000 |
| Rabbit Dermal Toxicity (mg/kg) | >5,000 | >5,000 | >5,000 | >5,000 |
| Rabbit Skin Irritation (ADIS) | 0.0 | 0.0 | 0.0 | 0.0 |
| Rabbit Eye Irritation | Mild to Moderate | Mild to Moderate | Mild to Moderate | Moderate |

[a] BioDynamics (1992a,b,c,d,e,f,g,h,i,j,k,l,m,n,o,p)

**Table 5: Dose Response from 90-day Inhalation Studies with Four DBEs**

| Exposure level | Test Materials | | | |
|---|---|---|---|---|
| ($mg/m^3$) | DMA[a] | DMG[a] | DMS[a] | DBE[b] |
| Control | | | | |
| 10 | -- | NOEC | -- | -- |
| 20 | -- | -- | -- | NOAEC[c] |
| 50 | -- | Significant effects | -- | -- |
| 80 | -- | -- | -- | Significant effects |
| 400 | Significant effects | Significant effects | Significant effects | Significant effects |

[a] Dupont (2000)

[b] Dupont Co. (1987), Keenan, C.M. et al. (1988), Keenan, C.M. et al. (1990)

**Table 6: Response of Rats Following Exposure to 400 mg/m$^3$ of Four DBE's for 90-days by Inhalation.**

| Test materials | DMA[a] | DMG[a] | DMS[a] | DBE[b] |
|---|---|---|---|---|
| **Nominal Concentrations** | 390 mg/m$^3$ | 410 mg/m$^3$ | 400 mg/m$^3$ | 390 mg/m$^3$ |
| **Effects/endpoints** | | | | |
| Mortality | N | N | N | N |
| Food consumption | ↓ | ↓ | N | N |
| Food Efficiency | ↓ | N | N | |
| Mean body weight | ↓ | ↓ | N | |
| Mean bodyweight gain | ↓ | ↓ | N | |
| Clinical signs of toxicity | N | N | N | N |
| Clinical pathology | N | N | N | -- |
| *Cell proliferation (CP)* | | | | |
| o Liver | ↑ | N | ↑ | ↑[C] |
| o Lungs | ↑ | N | N | -- |
| o Nose Level II | ↑ | ↑ | N | -- |
| o Nose Level III | N | ↑ | ↑ | -- |
| Neurobehavioral battery | N | N | N | -- |
| Neuropathology | N | N | N | -- |
| *Reproductive Endpoints* | | | | |
| o Sperm motility & morphology | N | N | N | -- |
| o Sperm count | N (increase not significantly different). | ↑ | ↑ | -- |
| o LH | N | ↑ | N | |
| o FSH | N | N | N | |
| o Testosterone | N | ↓ | N | -- |
| o Estradiol | N | N | ↓ | -- |
| o Progesterone | N | N | N | |
| o Estrous cycle | N | N | N | -- |
| *Effects on olfactory mucosa* | | | | |
| o Degradation & atrophy | ↑ | ↑ | ↑ | ↑ |
| o Focal respiratory metaplasia | ↑ | ↑ | ↑ | -- |

[a] Dupont (2000)

[b] Dupont Co. (1987), Keenan, C.M. et al. (1988), Keenan, C.M. et al. (1990)

[C] Observed effect based on increased liver weight without confirming cell proliferation.

## References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## Summary of DBE Category Robust Summaries

Dibasic esters (DBEs) are a solvent mixture of dimethyl succinate (DMS), dimethyl glutarate (DMG), and dimethyl adipate (DMA) or refined fractions of individual dimethyl esters. Physicochemical properties have been summarized as part of the Category Justification (above). DBEs are readily biodegradable with biodegradation half-lives of a few days. Model calculations indicate that DBEs photodegrade with half-lives of a few days to a few weeks. In water DBEs are predicted to be hydrolytically stable (half-life of > 2 years), but have a low potential for bioconcentration in aquatic organisms.

DBEs have very low acute oral toxicities with $LD_{50}$s in rats generally > 5,000 mg/kg (Category IV classification) with two exceptions reported as >500 and <5,000 mg/kg b.wt. for DBE (the mixture) and DMS, indicating possible Category III classification. By skin absorption, DBEs have a low order of acute toxicity to rabbits with dermal $LD_{50}$s of >5,000 mg/kg (Category IV). Based upon the most recent GLP studies DBEs are not considered to produce primary dermal irritation as defined in EPA Guidelines and are classified as Category IV. Earlier studies did show moderate irritation in one of six rabbits, but these results were not repeated in later studies. All four DBE materials are considered to produce eye irritation as defined by EPA Guidelines. Mild to moderate irritation involving the cornea was observed in rabbits with recovery by 7 days. This is consistent with Category III classification. DBEs are not skin sensitizers, and are not Class B poisons via skin or inhalation exposures. DBE is slightly toxic by inhalation with 1- and 4-hour LC50s in rats of > 10.7 and > 11 mg/L, respectively. In subchronic inhalation studies with all four DBEs, degeneration of the olfactory epithelium of the nose was observed. This change in the nasal tissues is related to enzymatic hydrolysis of DBE within the nasal cavity. However, risk to human nasal tissue due to DBE toxicity is likely to be reduced when compared to rats since DBEs are hydrolyzed more slowly in humans. No information is available on the carcinogenic potential of DBEs. A range of studies with DMS, DMG, DMA and DBE did not produce genetic damage in animals or bacterial cell cultures. DBE was positive in one study with cultured mammalian cells, but the positive findings were not apparent when the assay was repeated. Testing in rats indicates DBEs are not developmental or reproductive toxicants. In aquatic organisms, DBEs are “slightly” to “practically non-toxic” in fish and aquatic invertebrates.

## Test Plan for the Dibasic Esters Category

| No. | SIDS Data Elements | Data Available Y/N | Data Acceptable Y/N | Testing Required Y/N |
|---|---|---|---|---|
| **Physicochemical Properties** | | | | |
| 1 | Melting Point | Y | Y | N |
| 2 | Boiling Point | Y | Y | N |
| 3 | Vapor Pressure | Y | Y | N |
| 4 | Partition Coefficient | Y | Y | N |
| 5 | Water Solubility | Y | Y | N |
| 6 | Flash Point | Y | Y | N |
| **Environmental Fate** | | | | |
| 7 | Photodegradation | Y | Y | N |
| 8 | Stability in Water | Y | Y | N |
| 9 | Transport (Fugacity) | Y | Y | N |
| 10 | Biodegradation | Y | Y | N |
| 11 | Bioconcentration | Y | Y | N |
| **Ecotoxicology** | | | | |
| 12 | Acute Toxicity to Fish | Y | Y | N |
| 13 | Acute Toxicity to Daphnia | Y | Y | N |
| 14 | Acute Toxicity to Aquatic Plants | Y | Y | N |
| **Mammalian Toxicology** | | | | |
| 15 | Acute Toxicity | Y | Y | N |
| a | Acute Oral Toxicity | Y | Y | N |
| b | Acute Dermal Toxicity | Y | Y | N |
| c | Acute Inhalation Toxicity | Y | Y | N |
| d | Skin Irritation | Y | Y | N |
| e | Eye Irritation | Y | Y | N |
| 16 | Repeated Dose Toxicity | Y | Y | N |
| a | Oral | Y | Y | N |
| b | Inhalation | Y | Y | N |
| 17 | Developmental Toxicity | Y | Y | N |
| 18 | Reproductive Toxicity | Y | Y | N |
| 19 | *in vivo* Genotoxicity | Y | Y | N |
| 20 | *in vitro* Genotoxicity | Y | Y | N |